REMARKS

Claims 71 and 96-115 are under examination.

Withdrawn Claims

The Examiner has withdrawn claims 72, 116 and 117 from examination on grounds that they are directed to non-elected subject matter.

As to claims 116 and 117, Applicants note that the present application claims priority back to U.S. Patent 6,328,960 (hereafter, the '960), and that the pending claims herein track those of the '960 patent, with the insertion of "xenoantigen" in place of "alloantigen." Thus, claims 116 and 117 herein are counterparts of claims 21 and 22 of the '960 and Applicants believe that, for purposes of consistent prosecution, these should be examined along with the other claims pending herein. In addition, Applicants note that the Examiner has interposed a rejection herein based on obviousness-type double patenting over the '960 patent and therefore it might be intimated that this would extend to claims 116 and 117 herein with respect to claims 21 and 22 of the '960.

Applicants urge that claims 116 and 117 be rejoined with the other claims of the present case so as to avoid further delay in issuance of these claims when such was not the case in the matter of claims 21 and 22 of the '960 patent. This is especially appropriate in light of the obviousness-type double patenting rejection made herein based on the claims of the '960.

Objection to the Specification

The specification has been amended to reflect the current status of the parent applications: 09/427,333 and 09/267,536.

Rejection Under 35 U.S.C. 112, ¶2

Claims 99, 104, 108, 109 and 110-113 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

Claim 99 depends from claim 71 and recites that the T cells are present in a transplant. Claim 99 was rejected for insufficient antecedent basis because base claim 71 recites "transplant recipient" and not "transplant." In response, Applicant notes that it is not possible to have a transplant recipient without having a transplant. Applicant also notes that claim 77 is a similar claim to claim 5 of the issued parent (U.S. 6,328,960). Applicant also notes that it would be impossible to reduce an immune response of effector cells, such as T cells, of a transplant (claim 77) in a recipient unless this transplant were actually transplanted into the recipient. In the interest of advancing prosecution, Applicants have amended claim 71 to recite that the transplant recipient is a recipient of a transplant and claim 77 to recite that the T cells are present in said transplant.

Claim 104 recites "wherein the transplant is skin" and was rejected on similar grounds. In response, Applicants reiterate the above remarks in light of the amendment to claim 71, which now recites "a transplant."

Claim 108 recites "wherein the transplant is a solid organ" and was rejected on similar grounds. In response, Applicants reiterate the above remarks in light of the amendment to claim 71, which now recites "a transplant."

Claim 109 was rejected on unstated grounds but probably due to the fact that it depends on claim 108. In response, Applicants reiterate the above remarks in light of the amendment to claim 71, which now recites "a transplant."

Claims 110-113 recites different times for administration of the MSCs relative to the transplant and were rejected on similar grounds. In response, Applicants reiterate

the above remarks in light of the amendment to claim 71, which now recites "a transplant."

Rejection Under 35 U.S.C. 112, ¶1

Claims 71 and 96-115 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter not sufficiently described in the specification and representing new matter.

In addition, the Examiner notes at paragraph 3 of the Office Action that the filing date of the claims is deemed to be the filing date of the present application and not that of the parent applications, inviting the Applicants to present a detailed analysis of where the claims are supported in the application as filed.

Applicants respond to both contentions as follows.

The basic ground of rejection in both instances is that the claims recite a xenoantigen whereas the parent applications relate only to an alloantigen. In response, Applicants direct the Examiner's attention to U.S. Patent 6,368,636 (hereafter, the '636), which was filed on 26 October 1999 as Application Serial No. 09/427,333 and U.S. Patent 6,328,960, filed on 12 March 1999 as Application Serial No. 09/267,536.

The present application discloses that "Rejection of transplanted organs is significantly mediated by alloreactive T cells present in the host which recognize donor alloantigens or xenoantigens." (See application at page 2, lines 9-11, as well as U.S. Patent 6,368,636 at column 1, lines 49-51, and U.S. Patent 6,328,960, at column 1, line 47-49). This makes clear that rejection of transplants is due to T cells (or effector cells) that recognize donor alloantigens or xenoantigens, a reaction that the present invention is directed to reducing.

In addition, the present application teaches that "in accordance with preferred embodiments of the present invention, human mesenchymal stem cells are employed to treat transplant rejection and or graft versus host disease as a result of a transplant and or to prevent or reduce transplant rejection and or graft versus host disease. Human mesenchymal stem cells may also be employed to facilitate the use of xenogeneic grafts or transplants. It is also within the present invention to use xenogeneic cells, such as non-human primate cells, for the above purposes. " (emphasis added, see the application at page 6, lines 15-21, as well as U.S. Patent 6,368,636 at column 4, lines 16-24, and U.S. Patent 6,328,960, at column 4, line 9-16)

Thus, the application teaches use of MSCs to facilitate use of xenogeneic grafts or transplants (sources of xenoantigens) and is fully supported in the parent application, now the issued '636 patent.

In addition, the present application teaches that "the invention described herein provides for preventing or treating transplant rejection by administering the mesenchymal stem cells in a prophylactic or therapeutically effective amount for the prevention or treatment or amelioration of transplant rejection of an organ, tissue or cells from the same species, or a xenograft organ or tissue transplant and or graft versus host disease." (emphasis added, see application at page 15, lines 9-13, as well as U.S. Patent 6,368,636 at column 9, lines 12-18, and U.S. Patent 6,328,960, at column 8, line 12-18)

Thus, the present inventions teaches use of MSCs to preventing or treating transplant rejection involving a xenograft organ or tissue transplant, which is fully supported in the parent '636 patent.

In addition, the application teaches "suppression by baboon or human mesenchymal stem cells of a mixed lymphocyte reaction between human responder T

cells and baboon stimulator PBMC cells (donor 5909)." (see application at page 8, lines 18-20, describing Figure 13, as well as U.S. Patent 6,368,636 at column 5, lines 24-27)

Thus, the application teaches that an immune reaction (involving lymphocytes or effector cells) where the T cells are from human and the donor is baboon (thus, the reaction is xenogeneic and therefor involves a xenoantigen) can be suppressed by baboon or human MSCs.

Further, the application shows detailed support for such a method of using MSCs to suppress human T cell response to baboon PBMCs in Example 10, at page 43, lines 14-22 (and which is reproduced in the parent '636 patent at column 25, line 59, over to column 26, line 4).

Double Patenting Rejection

Claims 71 and 96-115 were rejected for obvious-ness type double patenting over claims 1-22 of U.S. Patent No. 6,328,960.

In response, Applicants note that the claims of the '960 are directed to alloantigen whereas the present claims are directed to xenoantigens. It is certainly possible to practice the present invention without reference to an alloantigen since allotransplants would be different from xenotransplants. However, to further prosecution, Applicants submit herewith a Terminal Disclaimer.

Rejection Under 35 U.S.C. 103

Claims 71 and 96-115 were rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/26470 in view of WO 96/23058. The Examiner argues that

the '470 discloses a method for reducing an immune response in a transplant recipient by administering suppressor cells while the '058 teaches a method for enhancing bone marrow engraftment by administering MSCs.

Initially, Applicants contend that whether these references can be combined to achieve the invention of the application is moot because the '470 is effective only as of its publication date, which is 19 April 2001, whereas the present application, as demonstrated above, is entitled to claim priority back to at least the filing date of the parent '636 patent, based on application Serial No. 09/427,333, filed 26 October 1999. Thus, the effective date of the present application is prior to the publication date of the WO '470, thereby removing it as a reference. In addition, because the WO '058 application only discloses use of MSCs along with bone marrow to enhance engraftment of the bone marrow transplant it does not either anticipate or render obvious the claimed invention.

Applicants also note that even if the references were combined, the result would be a method that comprises administering suppressor cells, MSCs and bone marrow, which does not produce the method recited by Applicants.

Applicants believe that no further argument is required. However, in the interests of a complete response, Applicants respectfully urge that even if both references could be relied on, there is no motivation to combine them and for several reasons.

1. The processes taught by each of the references is fundamentally different.

WO '470 teaches only the *in vitro* use of MSCs to produce suppressor cells, which suppressor cells are then administered to a recipient to suppress an immune reaction. There is no suggestion that the MSCs can be contacted with suppressor cells *in vivo* to accomplish anything. The Examiner merely assumes that this same result can be achieved *in vivo* because it is achieved by co-culturing, i.e., that one can simply substitute the *in vitro* reaction of the WO '470 for the *in vivo* reaction taught by

Applicants, without having to go through the co-culturing step and that it would be obvious to do so. Applicants respectfully contend that such a substitution is a major leap, especially where no evidence or art is offered to support such a suggestion.

The WO '058 discloses the administration of MSCs along with bone marrow cells to enhance engraftment of the bone marrow, as a means of treating cancer. As stated at page 2 of the WO '058, near the end of the middle paragraph, the MSCs migrate to the marrow cavity and differentiate into marrow stroma, thereby regenerating marrow stroma. There is no suggestion that the MSCs enhance engraftment by suppressing any immune response.

Because the MSCs in WO '058 are administered to enhance engraftment by regenerating stroma while the MSCs in WO '470 are used only *in vitro* to produce suppressor cells from T cells, which reactions are completely different, there is no reason to combine these references.

2. There is no motivation to combine the references because such combination would not be expected to achieve Applicants' claimed invention (i.e., suppression of an immune reaction). There are at least 2 reasons for this:

A. The WO '470 teaches the use of MSCs to "induce allo-activated T-cells to become suppressive for allogeneic purposes" (see the WO '470 at page 2, lines 18-19) and this is accomplished by co-culturing MSCs with activated T cells over a 4 day period (see WO '470 at page 13, line 2) with no other cells present in the culture.

Conversely, WO '058 states that after administration, MSCs migrate or home to the marrow and begin differentiating into marrow stroma (see WO '058 at page 2, near end of middle paragraph).

Based on the foregoing, those in the art would expect that, once administered, the MSCs would home to the marrow and differentiate into stroma and be unavailable for inducing activated T cells to become suppressor cells (the latter reaction only being possible because the MSCs and T cells are isolated in a culture medium with no other tissues or cells present and nowhere for the MSCs to migrate to).

Nor does WO '470 teach the effect of other cells and conditions on the ability of MSCs to induce activated T cells to become suppressor cells, except that this occurs after length co-culture with no other cells present. For example, such results might be achieved *in vitro* because the MSCs release some chemical that is permitted to build up to high levels in the co-culture, a result that might never be achieved *in vivo* where the culture is the size of a human patient and the MSCs are busy homing to the marrow so that they can differentiate into stromal cells.

B. The WO '470 defines suppressor T cells as "T cells which have been primed...by exposure to an alloantigen, and subsequently cultured with mesenchymal stem cells." (see WO '470 at page 6, lines 22-24). Thus, the effect of the MSCs is only on T cells activated by exposure to alloantigen (i.e., exposure to the transplant) but WO '058 suggests (at page 2, last paragraph) that the MSCs could be administered at any time relative to the transplant, even before the bone marrow (i.e., before the T cells were primed by exposure to alloantigen). Again, there is no motivation to combine these references.

For the foregoing reasons, Applicants contend that the WO '470 is not available as a reference against the present application and that, even if available, there is no motivation to combine it with WO '058 and that, even if combined, they do not achieve Applicants' claimed invention. In addition, neither of the cited references, alone or in combination, offer any evidence that any of the disclosed procedures, either alone or in combination, would be useful in reducing an immune response against a xenoantigen.

Conversely, Applicants do disclose this, along with appropriate data (see Applicants' Example 10 and Figure 13).

Applicants believe that all grounds of rejection have been overcome and respectfully request that the Examiner reconsider the patentability of the claims pending herein.

Applicants have included herewith a Request for a 3 month extension of time to respond to this Office Action as well as a check for the required fee for a small entity plus the fee for the terminal disclaimer. No additional fee is due in filing this response. Applicants request that the Commissioner charge any additional fee for this response, or credit any overpayment, to Deposit Acct. No. 03-0678.

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Alan J. Grant 7/29/04

Alan J. Grant, Esq. **Date**

Respectfully submitted,

Alan J. Grant

Alan J. Grant, Esq.
Reg. No. 33,389

CARELLA, BYRNE BAIN, GILFILLAN,
CECCHI, STEWART & OLSTEIN
Six Becker Farm Road
Roseland, NJ 07068
Phone: 973-994-1700
Fax: 973-994-1744